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(54) Title: ANDROGEN MODULATORS

(57) Abstract: The present invention is directed to the compound 4-(2-methoxy-phenoxy)-2-trifluoromethyl-benzonitrile, is use as an androgen modulator and to pharmaceutical compositions containing this compound.

WO 2006/018732 A1

ANDROGEN MODULATORS

FIELD OF THE INVENTION

The present invention is directed to a new phenoxybenzonitrile and to its use as an androgen receptor modulator. Other aspects of the invention are directed to the use of this compound to decrease sebum secretion and to stimulate hair growth.

BACKGROUND OF THE INVENTION

Alopecia, or balding, is a common problem which medical science has yet to alleviate. While androgens are associated with balding, the physiological mechanism by which this hair loss occurs is not known. However, it is known that hair growth is altered in individuals afflicted with alopecia.

Hair does not grow continuously but undergoes cycles of activity involving periods of growth, rest, and shedding. The human scalp typically contains from 100,000 to 350,000 hair fibers or shafts, which undergo metamorphosis in three distinct stages:

(a) during the growth phase (anagen) the follicle (i.e. the hair root) penetrates deep into the dermis with the cells of the follicle dividing rapidly and differentiating in the process of synthesizing keratin, the predominant component of hair. In non-balding humans, this growth phase lasts from one to five years;

(b) the transitional phase (catagen) is marked by the cessation of mitosis and lasts from two to three weeks; and

(c) the resting phase (telogen) in which the hair is retained within the scalp for up to 12 weeks, until it is displaced by new follicular growth from the scalp below.

In humans, this growth cycle is not synchronized. An individual will have thousands of follicles in each of these three phases. However, most of the hair follicles will be in the anagen phase. In healthy young adults, the anagen to

telogen ratio can be as high as 9 to 1. In individuals with alopecia, this ratio is reduced to as low as 2:1.

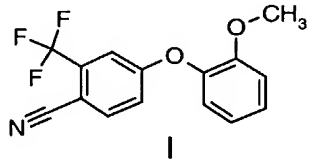
Androgenetic alopecia arises from activation of an inherited sensitivity to circulating androgenic hormones. It is the most common type of alopecia. It affects both men (50%) and women (30%), primarily of Caucasian origin. Gradual changes in the width and length of the hair shaft are experienced over time and with increasing age, prematurely in some. Terminal hair is gradually converted to short, wispy, colorless vellus hair. As a consequence, men in there 20's and women in their 30's and 40's begin to notice their hair becoming finer and shorter. In males, most of the hair loss occurs at the crown of the head. Females experience a thinning over their entire scalp. As discussed above, the anagen to telogen ratio is reduced significantly, resulting in less hair growth.

Minoxidil, a potassium channel opener, promotes hair growth. Minoxidil is available commercially in the United States under the trademark, Rogaine®. While the exact mechanism of action of minoxidil is unknown, its impact on the hair growth cycle is well documented. Minoxidil promotes the growth of the hair follicle and increase the period of time that the hair follicle is in the anagen phase (i.e., increases the anagen to telogen ratio).

While minoxidil promotes hair growth, the cosmetic efficacy of this growth can vary widely. For example, Roenigk reported the results of a clinical trial involving 83 males who used a topical solution of 3% minoxidil for a period of 19 months. Hair growth occurred in 55% of the subjects. However, only 20% of the subjects considered the growth to be cosmetically relevant. (Clin.Res., 33, No. 4, 914A, 1985). Tosti reported cosmetically acceptable re-growth in 18.1% of his subjects. (Dermatologica, 173, No. 3, 136-138, 1986). Thus, the need exists in the art for compounds having the ability produce higher rates of cosmetically acceptable hair growth in patients with alopecia.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new phenoxybenzonitrile has been discovered. This compound, its salts, hydrates, solvates, and prodrugs thereof, may be represented by Formula I below. It may also be referred to as 4-(2-methoxy-phenoxy)-2-trifluoromethyl-benzonitrile.



I

The compound of Formula I is an androgen receptor modulator. It has affinity for the androgen receptor and will cause a biological effect by binding to the receptor. Typically, it will act as antagonist. In selected embodiments, it may act as a tissue selective agonist. The compound can be used to treat, or alleviate, conditions associated with inappropriate activation of the androgen receptor. Examples of such conditions include, but are not limited to, acne, excess sebum secretion, androgenic alopecia, hormone dependant cancers such as prostrate cancer, and hirsutism.

The invention is also directed to pharmaceutical compositions containing the compound, in an amount effective to modulate activation of the androgen receptor. In a further embodiment, the invention is directed to an article of manufacture containing the compound, packaged for retail distribution, in association with instructions advising the consumer on how to use the compound to alleviate a condition associated with inappropriate activation of the androgen receptor. An additional embodiment is directed to the use of a compound as a diagnostic agent to detect inappropriate activation of the androgen receptor.

In a further embodiment, the compound is used topically to induce and/or stimulate hair growth and/or to slow down hair loss. The compound may also be used topically in the treatment of excess sebum and/or of acne.

DETAILED DESCRIPTION OF THE INVENTION

The headings within this document are only being utilized expedite its review by the reader. They should not be construed as limiting the invention or claims in any manner.

Definitions and Exemplification

As used throughout this application, including the claims, the following terms have the meanings defined below, unless specifically indicated otherwise.

The plural and singular should be treated as interchangeable, other than the indication of number:

a. "androgen" refers to testosterone and its precursors and metabolites, and 5-alpha reduced androgens, including but not limited to dihydrotestosterone. Androgen refers to androgens from the testis, adrenal gland, and ovaries, as well as all forms of natural, synthetic and substituted or modified androgens.

b. "pharmaceutically acceptable" means suitable for use in mammals.

c. "salts" is intended to refer pharmaceutically acceptable salts and to salts suitable for use in industrial processes, such as the preparation of the compound.

d. "pharmaceutically acceptable salts" is intended to refer to "pharmaceutically acceptable acid addition salts".

e. "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compound represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid

metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids, which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents, and which in comparison to their free base forms, generally demonstrate higher melting points.

f. "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

g. "compound of Formula I", "compounds of the invention", "compound", and "compounds" are used interchangeably throughout the application and should be treated as synonoms.

h. "patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, stump tail macques, and humans.

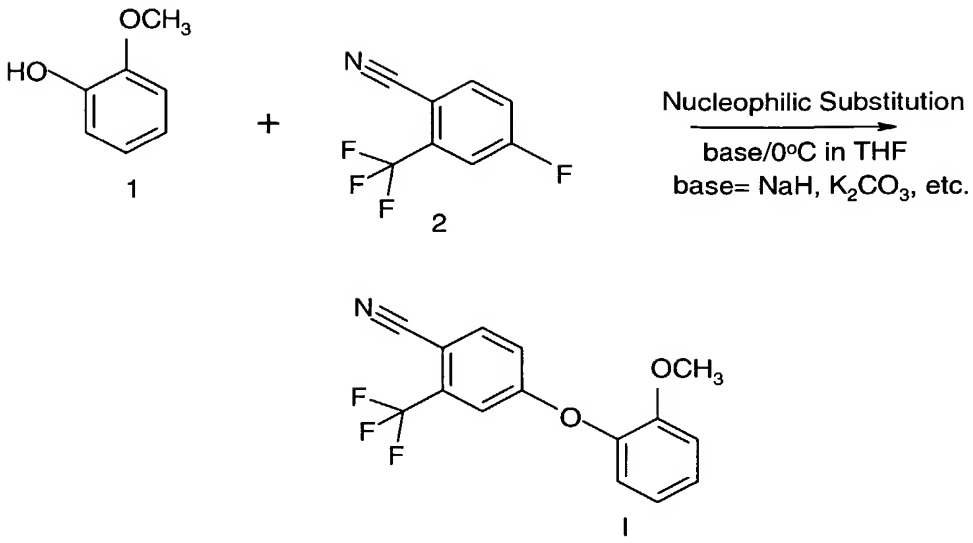
i. "treat" refers to the ability of the compound to either relieve, alleviate, or slow the progression of the patient's disease (or condition) or any tissue damage associated with the disease.

The compound of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention. The compound may also exist in one or more crystalline states, i.e. polymorphs, or they may exist as amorphous solids. All such forms are encompassed by the claims.

Synthesis

The compound of Formula I can be prepared using methods known in the art for the preparation of ethers. The reader's attention is directed to European Patent Application Number 58932, published September 1, 1982, the contents of which are hereby incorporated by reference for a description of such reactions. Scheme I below provides an overview of one such technique:

SCHEME I



As depicted above, one of the starting materials is the alcohol as depicted by structure 1. This alcohol is known in the art and may be purchased from known commercial sources. Alternatively, it may be prepared as described in the literature.

The other starting material is the 4-fluoro-benzonitrile depicted by structure 2. This benzonitrile is known in the art and may be synthesized as described by Japanese Patent Application Number 01097937.

The nucleophilic substitution depicted above may be carried out as is known in the art. The alcohol of structure 1 is contacted with a slight excess of a base, such as sodium hydride, potassium t-butoxide, potassium carbonate, etc., to produce an alkoxide ion. The reaction is carried out in an aprotic solvent, such as tetrahydrofuran, under an inert atmosphere (typically nitrogen) at a temperature of about 0°C. The alcohol is stirred with the base for a period of time ranging from 5 to 60 minutes.

One equivalent of the 4-fluoro-benzonitrile of structure 2 is then added to the reaction medium and the reactants are stirred for a sufficient period of time to allow the alkoxide ion to displace the fluorine from the benzonitrile. This typically

takes from 30 minutes to 24 hours. The reaction is typically allowed to warm to room temperature.

The desired product of Formula I can be recovered by extraction, evaporation, or other techniques known in the art. It may then be optionally purified by chromatography, recrystallization, distillation, or other techniques known in the art.

As would be appreciated by those skilled in the art, some of the methods useful for the preparation of such compounds, as discussed above, may require protection of a particular functionality, e.g., to prevent interference by such functionality in reactions at other sites within the molecule or to preserve the integrity of such functionality. The need for, and type of, such protection is readily determined by one skilled in the art, and will vary depending on, for example, the nature of the functionality and the conditions of the selected preparation method. See, e.g., T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The compound of this invention may form salts with pharmaceutically acceptable anions. All such salts are within the scope of this invention and they can be prepared by conventional methods such as combining the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate. The compound is obtained in crystalline form according to procedures known in the art, such as by dissolution in an appropriate solvent(s) such as ethanol, hexanes or water/ethanol mixtures.

Medical and Cosmetic Uses

The compound is an androgen receptor modulator. It can be used to alleviate conditions associated with inappropriate activation of the androgen receptor. More specifically, the compound is an androgen antagonist and may be used to treat, or alleviate, hormone dependent cancers such as prostate

carcinomas, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, hypertrichosis, precocious puberty, prostamegaly, virilization, and polycystic ovary syndrome.

In order to exhibit the therapeutic properties described above, the compound should be administered in a quantity sufficient to modulate activation of the androgen receptor. This amount can vary depending upon the particular disease/condition being treated, the severity of the patient's disease/condition, the patient, the particular compound being administered, the route of administration, and the presence of other underlying disease states within the patient, etc. When administered systemically, the compound typically exhibits its effect at a dosage range of from about 0.1 mg/kg/day to about 100 mg/kg/day for any of the diseases or conditions listed above. Repetitive daily administration may be desirable and will vary according to the conditions outlined above.

The compound may be administered by a variety of routes. It may be administered orally. The compound may also be administered parenterally (i.e., subcutaneously, intravenously, intramuscularly, intraperitoneally, or intrathecally), rectally, or topically.

In a typical embodiment, the compound is administered topically. Topical administration is especially appropriate for hirsutism, alopecia, acne and excess sebum. The dose will vary, but as a general guideline, the compound will be present in a dermatologically acceptable carrier in an amount of from about 0.01 to 50 w/w%, and more typically from about 0.1 to 10 w/w%. The dermatological preparation will be applied to the affected area from 1 to 4 times daily. "Dermatologically acceptable" refers to a carrier which may be applied to the skin or hair, and which will allow the drug to diffuse to the site of action. More specifically, it refers the site where inhibition of activation of an androgen receptor is desired.

In a further embodiment, the compound is used topically to relieve alopecia, especially androgenic alopecia. Androgens have a profound effect on both hair growth and hair loss. In most body sites, such as the beard and pubic skin, androgens stimulate hair growth by prolonging the growth phase of the hair cycle (anagen) and increasing follicle size. Hair growth on the scalp does not

require androgens but, paradoxically, androgens are necessary for balding on the scalp in genetically predisposed individuals (androgenic alopecia) where there is a progressive decline in the duration of anagen and in hair follicle size. Androgenic alopecia is also common in women where it usually presents as a diffuse hair loss rather than showing the patterning seen in men.

While the compound will most typically be used to alleviate androgenic alopecia, the invention is not limited to this specific condition. The compound may be used to alleviate any type of alopecia. Examples of non-androgenic alopecia include alopecia areata, alopecia due to radiotherapy or chemotherapy, scarring alopecia, stress related alopecia, etc. As used in this application, "alopecia" refers to partial or complete hair loss on the scalp.

Thus, the compound can be applied topically to the scalp and hair to prevent, or alleviate balding. Further, the compound can be applied topically in order to induce or promote the growth of hair on the scalp.

In a further embodiment of the invention, the compound is applied topically in order to prevent the growth of hair in areas where such hair growth is not desired. One such use will be to alleviate hirsutism. Hirsutism is excessive hair growth in areas that typically do not have hair (i.e. a female face). Such inappropriate hair growth occurs most commonly in women and is frequently seen at menopause. The topical administration of the compounds will alleviate this condition leading to a reduction, or elimination of this inappropriate, or undesired, hair growth.

The compound may also be used topically to decrease sebum production. Sebum is composed of triglycerides, wax esters, fatty acids, sterol esters and squalene. Sebum is produced in the acinar cells of the sebaceous glands and accumulates as these cells age. At maturation, the acinar cells lyse, releasing sebum into the lumenal duct so that it may be deposited on the surface of the skin.

In some individuals, an excessive quantity of sebum is secreted onto the skin. This can have a number of adverse consequences. It can exacerbate acne, since sebum is the primary food source for *Propionbacterium acnes*, the

causative agent of acne. It can cause the skin to have a greasy appearance, typically considered cosmetically unappealing.

Formation of sebum is regulated by growth factors and a variety of hormones including androgen. The cellular and molecular mechanism by which androgens exert their influence on the sebaceous gland has not been fully elucidated. However, clinical experience documents the impact androgens have on sebum production. Sebum production is significantly increased during puberty, when androgen levels are there highest. Anti-androgens, such as finasteride, have been shown to decrease androgen secretion. For additional information on sebum production and androgens role in skin metabolism, see Moshell et al, Progress in Dermatology, vol. 37, No. 4, Dec. 2003.

Thus, the compound inhibits the secretion of sebum and reduces the amount of sebum on the surface of the skin. The compound can be used to treat a variety of dermal diseases such as acne or seborrheic dermatitis.

In addition to treating diseases associated with excess sebum production, the compound can also be used to achieve a cosmetic effect. Some consumers believe that they are afflicted with overactive sebaceous glands. They feel that their skin is oily and thus unattractive. These individuals can utilize the compound of Formula I to decrease the amount of sebum on their skin. Decreasing the secretion of sebum will alleviate oily skin in individuals afflicted with such conditions.

Co-Administration

In a further embodiment of the invention, the compound can be co-administered with other compounds to further enhance its activity, or to minimize potential side effects. For example, potassium channel openers, such as minoxidil, are known to stimulate hair growth and to induce anagen. Examples of other potassium channel openers include (3S,4R)-3,4-dihydro-4-(2,3-dihydro-2-methyl-3-oxopyridazin-6-yl)oxy-3-hydroxy-6-(3-hydroxyphenyl)sulphonyl-2,2,3-trimethyl-2H-benzo[b]pyran, diaxozide, and P1075 which is under development

by Leo Pharmaceuticals. Such compounds can be co-administered with the compound of Formula I to alleviate alopecia

Thyroid hormone is also known to stimulate hair growth. Synthetic thyroid hormone replacements (i.e., thyromimetics) have also been shown to stimulate hair growth. Such thyromimetics have been described in the literature previously. The reader's attention is directed to European Patent Application No. 1262177, the contents of which are hereby incorporated by reference, for a discussion of such compounds and their use to alleviate alopecia. One particular compound of interest is 2-{4-[3-(4-Fluoro-benzyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-2H-[1,2,4]triazine-3,5-dione. Such compounds can be co-administered with the compound of Formula I to alleviate alopecia.

Anti-androgens can work by a number of different mechanisms. For example, some compounds block the conversion of testosterone to 5-α-dihydrotestosterone, which is responsible for the biological effect in many tissues. 5-Alpha-reductase inhibitors, such as finasteride, have been shown to stimulate hair growth and to decrease sebum production. Finasteride is commercially available from Merck under the trade name Propecia®. Examples of other 5-α-reductase inhibitors include dutasteride (Glaxo Smithkline). Such compounds can be co-administered with the compound of Formula I to alleviate alopecia and/or to decrease sebum production.

Protein kinase C inhibitors have also been shown to stimulate hair growth and induce anagen. Calphostin C, which is a selective inhibitor of protein kinase C, has been shown to induce anagen. Other selective protein kinase C inhibitors, such as hexadecylphosphocholine, palmitoyl-DL-carnitine chloride, and polymyxin B sulfate have also been shown to induce anagen. [Skin Pharmacol Appl Skin Physiol 2000 May-Aug;13(3-4):133-42]. Any such protein kinase C inhibitor can be co-administered with the compound of Formula I to alleviate alopecia.

Immunophilins are a family of cytoplasmic proteins. Their ligands include cyclosporin, and FK506. They are derived from fungi and were developed primarily for their potent immunosuppressive properties. Cyclosporin binds to the proteins, cyclophilins, while FK506 binds to FK binding proteins (FKBPs). All of these compounds have been shown to stimulate hair growth and induce anagen.

Any such immunophilin ligands can be co-administered with the compound of Formula I to alleviate alopecia.

Acyl CoA cholesterol acyl transferase (ACAT) inhibitors were initially evaluated for the treatment of elevated serum cholesterol. It was subsequently discovered that these compounds decrease sebum production (United States Patent No. 6,133,326). Any such ACAT inhibitor can be co-administered with the compound of formula I to decrease sebum production, alleviate oily skin, etc.

Antibiotics, such as tetracycline and clindamycin, have been used to alleviate acne. The antibiotic eradicates the microorganism, *Propionbacterium acnes,* leading to a reduction in the patient's acne. The compound of Formula I can be co-administered with any antibiotic suitable for the treatment of acne.

Retinoids, such as isotretinoin, have been shown to decrease sebum production and are used to treat acne. These retinoids can be co-administered with the compound of Formula I in order to decrease sebum production and/or to treat acne.

Estrogen and progesterone have each been shown to decrease sebum production. These compounds, or any synthetic agonist of such compounds, may be co-administered with the compound of formula I in order to decrease sebum production.

As used in this application, co-administered refers to administering the compound of Formula I with a second medicinal, typically having a differing mechanism of action, using a dosing regimen that promotes the desired result. This can refer to simultaneous dosing, dosing at different times during a single day, or even dosing on different days. The compounds can be administered separately or can be combined into a single formulation. Techniques for preparing such formulations are described below.

Formulations

If desired, the compound can be administered directly without any carrier. However, to ease administration, it will typically be formulated into pharmaceutical carriers. Likewise, it will most typically be formulated into dermatological, or cosmetic carriers. In this application the terms "dermatological

carrier" and "cosmetic" carrier are being used interchangeably. They refer to formulations designed for administration directly to the skin or hair.

Pharmaceutical and cosmetic compositions can be manufactured utilizing techniques known in the art. Typically an effective amount of the compound will be admixed with a pharmaceutically/cosmetically acceptable carrier.

For oral administration, the compound can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions, or emulsions. Solid unit dosage forms can be capsules of the ordinary gelatin type containing, for example, surfactants, lubricants and inert fillers such as lactose, sucrose, and cornstarch or they can be sustained release preparations.

In another embodiment, the compound of Formula I can be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders, such as acacia, cornstarch, or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate. Liquid preparations are prepared by dissolving the active ingredient in an aqueous or non-aqueous pharmaceutically acceptable solvent, which may also contain suspending agents, sweetening agents, flavoring agents, and preservative agents as are known in the art.

For parenteral administration, the compound may be dissolved in a physiologically acceptable pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable pharmaceutical carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative, or synthetic origin. The pharmaceutical carrier may also contain preservatives, buffers, etc., as are known in the art. When the compound is being administered intrathecally, it may also be dissolved in cerebrospinal fluid as is known in the art.

The compound of this invention will typically be administered topically. As used herein, topical refers to application of the compounds (and optional carrier) directly to the skin and/or hair. The topical composition according to the present invention can be in the form of solutions, lotions, salves, creams, ointments,

liposomes, sprays, gels, foams, roller sticks, or any other formulation routinely used in dermatology.

Thus, a further embodiment relates to cosmetic or pharmaceutical compositions, in particular dermatological compositions, which contain the compound. Such dermatological compositions will contain from 0.001% to 10% w/w% of the compound in admixture with a dermatologically acceptable carrier, and more typically, from 0.1 to 5 w/w% of the compound. Such compositions will typically be applied from 1 to 4 times daily. The reader's attention is directed to Remington's Pharmaceutical Science, Edition 17, Mack Publishing Co., Easton, PA for a discussion of how to prepare such formulations.

The compositions according to the invention can also consist of solid preparations constituting cleansing soaps or bars. These compositions are prepared according to the usual methods.

The compound can also be used for the hair in the form of aqueous, alcoholic or aqueous-alcoholic solutions, or in the form of creams, gels, emulsions or mousses, or alternatively in the form of aerosol compositions also comprising a propellant under pressure. The composition according to the invention can also be a hair care composition, and in particular a shampoo, a hair-setting lotion, a treating lotion, a styling cream or gel, a dye composition, a lotion or gel for preventing hair loss, etc. The amounts of the various constituents in the dermatological compositions according to the invention are those conventionally used in the fields considered.

The medicinal and cosmetics containing the compound will typically be packaged for retail distribution (i.e. an article of manufacture or a kit). Such articles will be labeled and packaged in a manner to instruct the patient how to use the product. Such instructions will include the condition to be treated, duration of treatment, dosing schedule, etc.

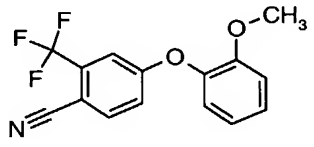
The compound of Formula I may also be admixed with any inert carrier and utilized in laboratory assays in order to determine the concentration of the compounds within the serum, urine, etc., of the patient as is known in the art. The compound may also be used as a research tool.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention. The following examples and biological data are being presented in order to further illustrate the invention. This disclosure should not be construed as limiting the invention in any manner.

EXAMPLES

EXAMPLE 1A

4-(2-Methoxy-phenoxy)-2-trifluoromethyl-benzonitrile



To a Bohdan mini-block reaction tube containing a solution of 4-fluoro-2-(trifluoromethyl)-benzonitrile (0.25mmol) and 2-methoxy-phenol (0.25 mmol) in anhydrous dimethylformamide "DMF" (1.25mL) was added 1mL of a 0.85M slurry of sodium hydride (60% dispersion in mineral oil) in anhydrous DMF (3.4eqs, 0.85mmol). The Bohdan mini-block was capped and the reaction was shaken at room temperature for 18hours("h"). 500 microliters "μL" of methanol and 210mgs of macroporous tosic acid resin "MP-TsOH" (4.07 mmol/g, 3.4eq, 0.85 mmol) was added and the reaction was shaken at ambient temperature 20h. Reaction was filtered, washing solids well with methanol, and concentrated utilizing a nitrogen blow down rack then a rotoevaporator, Genevac HT-12. Sample was purified via reverse phase HPLC (BHK 30x100mm ODS-O/B C18

5um; A=acetonitrile/3% propanol, B=water/3% 1-propanol; 0-6.5min: 15% A, 85%B, 6.5-10.5min: 100%A).

MS: 294.16 (M+1 for $C_{15}H_{10}F_3NO_2$); RT 3.74, Purity: 100

LCMS: Atlantis C18 50mm x 4.6mm, 3mm column (Solvent: A=Water w/ 0.005M Formic Acid; B=Acetonitrile w/0.005M Formic Acid, Method: 0-3 min: 85% A, 15% B; 3-5.1 min: 2% A, 98% B; 5.1-7 min: 85% A, 15% B

EXAMPLE 1B

This example illustrates an alternative preparation of 4-(2-methoxy-phenoxy)-2-trifluoromethyl-benzonitrile. To 500 ml of acetonitrile was added 36.7 grams("g") of 4-fluoro-2-(trifluoromethyl)-benzonitrile, 30g of potassium carbonate, and 22g of 2-methoxy-phenol. The admixture was heated at reflux for approximately 5.5 h. In process NMR was carried out which showed ~15% 4-fluoro-2-(trifluoromethyl)-benzonitirle and 10% 2-methoxy-phenol. An additional 1 ml of 2-methoxy-phenol was added and the admixture was stirred at reflux for an additional 2h (approximately). The admixture was cooled to approximately 30°C filtered, washed with acetonitrile and condensed to an oil.

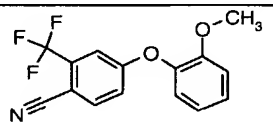
HNMR showed approximately 6% of un-reacted nitrile in this product. The next morning the product was contacted with 500 ml of acetonitrile, 1.2 ml of 2-methoxy-phenol, 1.8 g of potassium carbonate and heated to reflux for an additional 5 hours. 100 ml of heptane was then added and the admixture was cooled to 20°C and filtered. The filtrate was washed twice with 30 ml of acetonitrile and condensed to an oil which upon standing solidified. The solid was slurried in 50 ml of 1:1 isopropyl alcohol/water. It was dried at 50°C for 3 hours to give product.

HPLC 99.87%
CHN Theory: C, 61.44 ; H, 3.44; N, 4.78. Found: C, 61.28; H, 3.36; N, 4.75
MS: 294 (M+1 for $C_{15}H_{10}F_3NO_2$)

EXAMPLE 2

The compound of Formula I has affinity for the androgen receptor. This affinity has been demonstrated using the human receptor. The description below describes how the assay was carried out.

Competitive binding analysis was performed on baculovirus/Sf9 generated hAR extracts in the presence or absence of different concentrations of test agent and a fixed concentration of ^{3}H-dihydrotestosterone (^{3}H-DHT) as tracer. This binding assay method is a modification of a protocol previously described (Liao S. , et. al. J. Steroid Biochem. 20:11-17 1984). Briefly, progressively decreasing concentrations of compounds are incubated in the presence of hAR extract (Chang et al. P.N.A.S. Vol. 89, pp. 5546-5950, 1992), hydroxylapatite, and 1 nM ^{3} H-DHT for one hour at 4^{0}C. Subsequently, the binding reactions are washed three times to completely remove excess unbound ^{3} H-DHT. hAR bound ^{3}H-DHT levels are determined in the presence of compounds (i.e. competitive binding) and compared to levels bound when no competitor is present (i.e. maximum binding). Compound binding affinity to the hAR is expressed as the concentration of compound at which one half of the maximum binding is inhibited. Table I below provides the results that were obtained for the compound (reported data is the mean of multiple tests as shown below)

Example #	Structure	AR Binding IC_{50} (nM)
1		109 (N=4)

EXAMPLE 3

The ability of the compound to antagonize the effects of androgen on the androgen receptor were determined in a whole cell assay as described immediately below.

Experimental procedure for AR antagonist cell assay

Cell line: MDA-MB453-MMTV clone 54-19. This cell line is a stable transfected cell line with MDA-MB453 cell background (a human breast tumor cell line expressing androgen receptor). A MMTV minimal promoter containing ARE was first cloned in front of a firefly luciferase reporter gene. Then the cascade was cloned into transfection vector pUV120puro. Electroporation method was used for transfecting MDA-MB-453 cell. Puromycin resistant stable cell line was selected.

Cell culture media and reagents:

Culture medium: DMEM (high glucose, Gibco cat #: 11960-044), 10%FBS, and 1% L-glutamine

Plating medium: DMEM (phenol red free), 10% charcoal treated HyClone serum, 1% L-glutamine

Assay medium: DMEM (phenol red free), 1% charcoal treated HyClone serum, 1% L-glutamine, and 1% penicillin/streptomycin

3X luciferase buffer: 2% beta-mercaptoethanol, 0.6% ATP, 0.0135% luciferine in cell lysis buffer

Assay procedure:

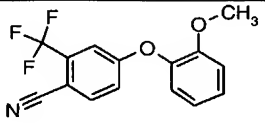
1. Cells are maintained in culture medium, splitting cells when they reach 80-90% confluence
2. To test compounds, 10,000 cells/well are plated to opaque 96 cell culture plate in 100 ul/well plating medium, culture for overnight at 37^0C in cell culture incubator
3. Carefully remove plating medium, then add 80 ul/well of pre-warmed assay medium, add 10 ul/well testing compound (final concentration at)

1000 nM, 200 nM, 40 nM, 8 nM, 1.6 nM, and 0.32 nM), incubate at 37°C for 30 minutes

4. Add 10 ul/well freshly prepared DHT (final concentration at 100 pM) to each well, incubate at 37°C for 17 hr (overnight)
5. Add 50 ul/well 3X luciferase buffer, incubate at room temperature for 5 minutes, then count on Luminometer

The fold induction over background by 100 pM DHT in the absence of testing compounds is standardized as 100% and experimental result is expressed as percentage of inhibition by testing compounds.

The results obtained with the compound are described below in Table III. The results are reported as the mean of multiple tests as described below (the numbers of tests are indicated in the footnote.

Example #	Structure	AR Cell IC50 (nM)
1		82 (N=4)

Example 4

Animal Model for Inhibition of Sebum Production

Luderschmidt et al describes an animal model for testing whether compounds are capable of modulating sebum secretion. Arch. Derm. Res. 258, 185-191 (1977). This model uses male Syrian hamsters, whose ears contain sebaceous glands. The product of Example 1 was screened in this model.

Testing for sebum inhibition was carried out in the following manner. Male Syrian hamsters aged 9 to 10 weeks were introduced into the laboratory environment and acclimated for 2 weeks prior to use in the study. Each group consisted of 5 animals and run in parallel with vehicle and positive controls. Prior

to administration, a sufficient quantity each compound was dissolved in 1 mL of a solvent consisting of ethanol, transcutanol, and propylene glycol (60/20/20 v/v/v)to achieve a final concentration of 3.0 w/v%.

Animals were dosed topically twice daily, five days a week, for 2 weeks. Each dose consisted of 25 micro liters of vehicle control or drug. The dose was applied to the ventral surfaces of both the right and left ears. All animals were sacrificed approximately 18-24 hours after the final dose. The right ears were collected from each animal and used for sebum analysis.

The ears were prepped for HPLC analysis in the following manner. One 8mm distal biopsy punch was taken, just above the anatomical "V" mark in the ear to normalize the sample area. The punch was pulled apart. The ventral biopsy surface (the area where the topical dose was directly applied to the sebaceous glands) was retained for testing and the dorsal surface of the biopsy punch was discarded.

Tissue samples were blown with N_2 gas and stored at -80°C under nitrogen until HPLC analysis. In addition to ear samples, an aliquot of each drug and vehicle (at least 250ul) was also stored at -80°C for inclusion in the HPLC analysis.

HPLC analysis was carried out on an extract of the tissue sample. Tissue samples were contacted with 3ml of solvent (a 4:1 admixture of 2,2,4-trimethylpentane and isopropyl alcohol). The mixture was shaken for 15 minutes and stored overnight at room temperature, protected from light. The next morning 1 milliliter of water was added to the sample and shaken for 15 minutes. The sample was then centrifuged at approximately 1500rpm for 15 minutes. Two ml of the organic phase (top layer) was transferred to a glass vial, dried at 37°C, under nitrogen, for approximately 1 hour, and then lyophilized for approximately 48 hours. The samples were then removed from the lyophilizer and each vial was reconstituted with 600µl of solvent A (trimethylpentane/tetrahydrofuran (99:1). The samples were then recapped and vortexed for 5 minutes.

200µl of each sample was then transferred to a pre-labeled 200µl HPLC vial with 200 µL glass inserts. The HPLC vials were placed in the autosampler tray for the Agilent 1100 series HPLC unit. The Agilent 1100 HPLC system consisted of a thermostated autosampler, a quarternary pump, a column heater, and an A/D interface module. All components were controlled by Agilent ChemStation software. A Waters Spherisorb S3W 4.6x100 mm analytical column was maintained at 30°C by the Agilent column heater unit. The HPLC autosampler was programmed to maintain the sample temperature at 20C throughout the run.

10uL of each sample was injected in triplicate into the column. Two solvents were used for the solvent gradient. Solvent A was an admixture of trimethylpentane and tetrahydrofuran (99:1). Solvent B was ethylacetate. The gradient utilized is described in the table below:

Time (min)	Solv A (%)	Solv B (%)	Flow (mL/min)
0	99	1	2
2	96	4	2
6	60	40	2
7	5	95	2
10	5	95	2
10.1	99	1	2

The Sedex 75 Evaporative Light Scattering Detector (ELSD) was operated at 45°C with a gain of 5, and N_2 pressure maintained at 3.1 bar. Analog signal obtained by the instrument was sent to the Agilent A/D interface module where it was converted to a digital output. The conversion was based on a 10000 mAU/volt set point and the data rate was set at 10Hz (0.03 min). The resulting digital output was then feed into the Agilent ChemStation software for integration of the peak area.

The results of the HPLC analysis are reported below in Table IV. The results are reported as the reduction in cholesterol ester (CE) and wax ester (WE) production, when compared to the vehicle control. A negative value reflects an increase in sebum, whereas a positive reflects a decrease.

Example #	% CE reduction	% WE reduction	Sum of CE & WE
1	27	51	79

EXAMPLE 5

Animal Model for Androgenetic Alopeica

As described above, alopecia is a problem that medical science has devoted considerable resources to. As with any disease process, animal models have been developed to allow scientists to screen compounds for their potential relative efficacy. Those compounds showing the greatest efficacy in these animal models are considered for further study in humans. Two different animal models have been developed to date for alopecia. The first is the telogen conversion assay, which uses female C3H/HeN mice. The second model uses stump-tailed macaques, which are monkeys that suffer from androgenetic alopecia.

The telogen conversion assay measures the potential of a compound to convert the resting stage of the hair growth cycle ("telogen") to the active stage of the hair growth cycle ("anagen") in mice. This assay takes advantage of the fact that the fur (i.e. hair) of 7-week-old C3H/HeN mice is in the telogen phase. This phase continues until about 75 days of age. In this assay, selected areas of the mice are shaved, contacted with a test agent, or a control, and the difference in the rate of hair growth is measured (i.e. induction of the anagen phase). The first sign of anagen is the darkening of skin color as melanocytes in the follicles start to synthesize melanin, in preparation for the production of pigmented hairs. This model has a number of advantages. This includes the ready availability of female CH3HeN mice, the ability to screen large numbers of compounds quickly, and the ease of housing and handling such animals.

The primary disadvantage of this model is its lack of androgenetic dependency. While the exact cause of human baldness is not known, it is well

documented that androgens induce a regression of hair follicles in the scalp. This post adolescent regressive change is a fundamental cause of male pattern baldness, (i.e. "androgenetic alopecia). This phenomenon occurs in both men and women who have inherited the genetic trait for alopecia, as mentioned previously. For a more detail discussion of the effects of androgens on human scalps, the readers attention is directed to Trueb, RM, Molecular Mechanisms of Androgenic Alopecia, Exp. Gerontology, 2002, 27:981-990.

Researchers looked for other animals whose hair growth was similar to that of humans. These lead researchers to stump-tailed macaques. These primates also suffer from androgenetic alopecia. Essentially all post adolescent macaques, in both sexes, exhibit the development of baldness. Like the development of male pattern baldness in humans, androgens are an indispensable triggering factor in macaque baldness. Thinning of the frontal scalp hairs begins to appear around the same age (4 years) when serum levels of testosterone become drastically elevated in male animals. Although the elevation of testosterone in females is approximately one tenth that of the male level, there is no difference in the incidence and the age of onset of baldness between male and female stump-tailed macaques. Topical application of anti-androgens have reversed this baldness in animals of both sexes (Pan, H J et al, Evaluation of RU58841 as an anti-androgen in prostate PC3 cells and a topical anti-alopecia agent in the bald scalp of stump tailed macaques. Endocrine 1998; 9:39-43).

While this model is a significant improvement over the telogen conversion assay as a model for human baldness, it suffers from a number of practical disadvantages. The macaques are expensive, relatively rare, labor intensive to maintain, and require long wash out periods between testing. Thus, the macaque is not a practical model for screening large numbers of compounds

It has been discovered that male C3H/HeN mice may be used in the telogen conversion assay, when evaluating anti-androgen test compounds. Thus, the model relates to a modification of the existing telogen conversion assay. Male C3H/HeN mice approximately 7 weeks old are utilized. These animals are also uniformly in telogen, like their female counterparts. However, once shaven, the androgens inherently present in these male mice inhibit the conversion of the

hair follicles to the anagen phase. An anti-androgen will block this androgenic effect and the follicles will convert to anagen, like their female counterparts.

EXAMPLE 5A

The compound described in Example 1 was submitted for further testing utilizing the modified telogen conversion assay, described above. The testing was carried out in the following manner.

Male C3H/HeN mice, 6 to 7 weeks old (Charles River Laboratories, Raleigh, NC) were used for the study. Fur was clipped from the dorsal region of the mice prior to initiation of the study. Only mice with pink skin, a visual indication of the telogen phase, were selected for inclusion in the study.

The test compound was dissolved in a vehicle consisting of propylene glycol (30%) and ethanol (70%) to achieve a concentration of 1% w/v. The relevant dose was applied topically to the clipped dorsal region of the mice in one test group (7-10 mice) in a volume of 20 $\mu l/cm^2$. A second group of animals received only the vehicle to serve as a control. Treatments were applied twice daily for 4 weeks.

The treatment area was observed and graded every other day for signs of hair growth. The hair growth response was quantified by recording, for each animal, the day on which signs of hair growth first appeared over the treated area. The first sign of anagen was the darkening of skin color as melanocytes in the follicles started to synthesize melanin in preparation for the production of pigmented hairs. The mice were observed for 35 days or longer.

Anagen was not initiated in the test group prior to its occurrence in the vehicle control group at a concentration of 1%(w/v).

CLAIMS

What is claimed is:

1. 4-(2-Methoxy-phenoxy)-2-trifluoromethyl-benzonitrile or a salt thereof.

2. A compound according to claim 1, present as a pharmaceutically acceptable salt.

3. Use of a compound according to claim 1 as a medicine.

4. Use of a compound according to claim 1 in the manufacture of a medicament for inhibiting activation of the androgen receptor.

5. Use of a compound according to claim 1 in the manufacture of a medicament for alleviating a condition selected from the group consisting of hormone dependent cancers, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, premenstrual syndrome, lung cancer, and precocious puberty.

6. Use of a compound according to claim 1 in the manufature of a medicament to alleviate a condition selected from the group consisting of acne, alopecia and oily skin.

7. A pharmaceutical composition comprising a compound according to claim 1 in admixture with one, or more, pharmaceutically acceptable excipients.

8. A topical pharmaceutical formulation comprising a compound according to claim 1 in admixture with one, or more, pharmaceutically acceptable excipients suitable for dermal application.

9. An article of manufacture comprising a compound according to claim 1 packaged for retail distribution, which advises a consumer how to utilize the compound to alleviate a condition selected from the group consisting of acne, alopecia, and oily skin.

INTERNATIONAL SEARCH REPORT

International Application No
I../IB2005/002832

A. CLASSIFICATION OF SUBJECT MATTER
C07C255/54 A61K31/277 A61P17/14 A61P17/08 A61Q7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/068217 A (ENDORECHERCHE, INC; LABRIE, FERNAND; SINGH, SHANKAR, MOHAN; LUU-THE, V) 21 August 2003 (2003-08-21) page 1, line 1 - page 2, line 21; claims; table 1	1-9
A	WO 03/074473 A (THE UNIVERSITY OF TENNESSEE RESEARCH CORPORATION; DALTON, JAMES; MILLE) 12 September 2003 (2003-09-12) page 7, line 16 - page 8, line 5; claims; examples	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 December 2005	09/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seufert, G

INTERNATIONAL SEARCH REPORT

:ernational application No.
PCT/IB2005/002832

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
I /IB2005/002832

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03068217 A	21-08-2003	AU 2003205461 A1	04-09-2003
		CA 2474171 A1	21-08-2003
		CN 1633287 A	29-06-2005
		EP 1474127 A1	10-11-2004
		JP 2005525337 T	25-08-2005
WO 03074473 A	12-09-2003	AU 2003214971 A1	16-09-2003
		CA 2476651 A1	12-09-2003
		HR 20040851 A2	28-02-2005